Environmental Exposures and Autism: Examining the Evidence

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Learning Objectives

1. Identify environmental exposures of concern to the maternal – fetal environment;
2. Reflect on toxic exposures in both indoor and outdoor environments;
3. Describe select measures and quality of scientific evidence;
4. Discuss gene-environment interactions as factors of risk and illness; and
5. Examine select environmental exposures in the scientific literature associated with autism.
Always
Unique
Totally
Interesting
Sometimes
Mysterious

Autism, Defined

“a developmental disorder that appears by age three and that is variable in expression but is recognized and diagnosed by impairment of the ability to form normal social relationships, by impairment of the ability to communicate with others, and by stereotyped behavior patterns especially as exhibited by a preoccupation with repetitive activities of restricted focus rather than with flexible and imaginative ones.”

Source: http://www.merriam-webster.com/medical/autism
ASD: Previously 5 disorders

- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSM-IV-TR) defined ASD as five disorders:
  - Autistic disorder (classic autism)
  - Asperger's disorder (Asperger syndrome)
  - Pervasive developmental disorder not otherwise specified (PDD-NOS)
  - Rett's disorder (Rett syndrome)
  - Childhood disintegrative disorder (CDD).

In DSM-5 diagnostic manual, all autism disorders were merged into one diagnosis of ASD.
CAUSE OF AUTISM

UNKNOWN
Prevalence

- About 1 in 6 children in the United States had a developmental disability in 2006-2008, ranging from mild disabilities such as speech and language impairments to serious developmental disabilities, such as intellectual disabilities, cerebral palsy, and autism;
- About 1 in 68 children has been identified with autism spectrum disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network; ASD is almost 5 times more common among boys (1 in 42) than among girls (1 in 189)
- Source: http://www.cdc.gov/ncbddd/autism/data.html
Updated information

- ASD reports are now 30% higher than the estimate for 2008 (1 in 88), roughly 60% higher than the estimate for 2006 (1 in 110), and roughly 120% higher than the estimates for 2002 and 2000 (1 in 150). Unsure what this is related to: identification, diagnosis, community influences?
- The number of children identified with ASD varied widely by community, from 1 in 175 children in areas of Alabama to 1 in 45 children in areas of New Jersey.
- Almost half (46%) of children identified with ASD had average or above average intellectual ability (IQ greater than 85).
- Source: http://www.cdc.gov/Features/dsautismdata/index.html
Differences and Demographics

- White children were more likely to be identified with ASD than black or Hispanic children. About 1 in 63 white children, 1 in 81 black children, and 1 in 93 Hispanic children were identified with ASD.
- Black and Hispanic children identified with ASD were more likely than white children to have intellectual disability.
- No difference among racial and ethnic groups in the age at which children were first diagnosed.
- About 80% of children identified with ASD either received special education services for autism at school or had an ASD diagnosis from a clinician. The remaining 20% of children identified with ASD had symptoms of ASD documented in their records, but had not yet been classified as having ASD by a community professional in a school or clinic.
- Source: [http://www.cdc.gov/Features/dsautismdata/index.html](http://www.cdc.gov/Features/dsautismdata/index.html)
Identification and Diagnosis

- Less than half (44%) of children identified with ASD were evaluated for developmental concerns by the time they were 3 years old.
- Most children identified with ASD were not diagnosed until after age 4, even though children can be diagnosed as early as age 2.

Source: http://www.cdc.gov/Features/dsautismdata/index.html
What causes autism?
Exploring the environmental contribution

- Hypothesis: “Early environmental exposures contribute to causation perhaps acting in concert with genetic susceptibilities…” (p.219)

- Variation in exposure type and genotype and function observed differences in the behavioral expression of autism

Landrigan (2010) continued

- Plausibility for an environmental contribution to causation of autism:
  - 1. Current understanding of the exquisite vulnerability of the developing human brain to toxic exposures in the environment; and
  - 2. Historically important, proof-of-concept studies that specifically link autism to environmental exposures experienced prenatally.
Some syndromes of autism are genetic, such as, single gene disorders, though rare, account for less than 5% of ASD cases.

Some children diagnosed with ASD have other uncategorized genetic mutations (not yet named as syndromes).

In aggregate they may account for 10 - 20 percent or more of cases defined within “autisms.”

No single gene that is a major new cause of autism; but variants do pose risk factors.

Congenital abnormalities

Acquired abnormalities

Genetic change (Mutation)

Epigenetic change (Abnormal switching)

Aberrant Expression of Synapse Genes

“Synaptic” Autism

Epigenetic change (Abnormal switching)

Environmental factors

Select Risk Factors

- Gardener et al. (2009)
- Advanced parental age at birth
- Maternal use of certain types of prenatal medications
- Maternal bleeding
- Gestational diabetes,
- Firstborn
- Mother who was born abroad.
Maternal-fetal environment

- How important is this environment?
- The in utero environment provides nutrients, gas-exchange, and our first “home” for shelter, as humans.
- Adverse conditions of the in utero environment can impact lifelong health.
Why study the maternal-fetal environment?

- Impaired fetal growth has been associated with adult conditions of cardiovascular disease, Type II diabetes mellitus, dyslipidemia, impaired glucose tolerance, and vascular endothelial dysfunction.
- These associations underscore the susceptibility of fetal growth to adverse uterine conditions; including alteration of gene expression, tissue and organ differentiation, homeostasis and possibly oxidative stress.
What conditions affect the maternal – fetal environment?

- For this lecture, we will be discussing select examples, such as:
  - Maternal smoking
  - Metals
  - Pesticides
  - Traffic-related pollutants
- Other:
  - Drugs: Thalidomide,
  - Perinatal complications
Critical Periods of Development

- Critical periods are times in development when the brain is particularly sensitive to social or physical environmental influences.

Critical periods in human development

- Period of dividing zygote, implantation & bilaminar embryo
- C.N.S.: heart, eye, heart, eye, ear, palate, ear, external genitalia
- Brain development stages (ages: 9, 16, 20-36, 38 weeks)
- Central nervous system susceptible
- Not susceptible to teratogens

- Prenatal death
- Major congenital anomalies (red)
- Functional defects & minor congenital anomalies (yellow)

* Red indicates highly sensitive periods when teratogens may induce major anomalies.
Factors associated with autism risk in the meta-analysis were abnormal presentation, umbilical-cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-minute Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia. Factors not associated with autism risk included anesthesia, assisted vaginal delivery, postterm birth, high birth weight, and head circumference.

Source: Gardener, et al (2011); Pediatrics; (doi: 10.1542/peds.2010-1036)
The effect of maternal smoking during pregnancy on children’s birth weight has been recognized since 1957 (Simpson).

The first reports concerning the adverse effects of environmental tobacco smoke (ETS) were published in the 1960’s.

Parameters of birthweight, length, and head circumference were found to be lower in children born to smoking mothers (Wang, 1997).
Kalkbrenner et al. (2012) reported a potential association between maternal smoking and higher functioning autism syndrome disorder (ASD) subtypes which warranted further studies.

Other studies had previously reported associations between maternal smoking and ASD (St. Pourcain et al. 2011) and between maternal smoking and attention deficit hyperactivity disorder (Langley et al. 2012).
Baron-Cohen (2002) proposed that one cause of autism is exposure to high levels of intrauterine testosterone;

Maternal source of testosterone (James, 2012) Stress causes women to secrete adrenal androgens including testosterone;

Androgen levels are reportedly high in women who smoke (Kaergaard et al. 2000; Pölkki and Rantala 2009; Sowers et al. 2001), and this has been specifically reported in pregnant women (Toriola et al. 2011).

Heavy Metals
Cadmium (Cd$^{+2}$)

- Metal found in the earth’s crust; frequent by-product from extraction of zinc, lead, and copper ores.
- May be found in: batteries, pigments, platings, plastic stabilizers, non-ferrous alloys and mining
Cd Exposure

- Cd emitted to air, soil, water from non-ferrous mining and may accumulate in agricultural crops;
- Tobacco leaves accumulate high levels of Cd from soil; and smoking is a major source of Cd;
- Each cigarette contains approximately 1-2 ug Cd
- Non-smokers may also be exposed to Cd through food sources.
- Smoking may double body burden of Cd exposure

Source: ATSDR: Public Health Statement on Cadmium
Cd and the Placenta

- Cadmium accumulates in the placenta in mothers exposed during pregnancy (Korpela, et al., 1986; Osman et al., 2000)
Metallothionein

- Low molecular weight, cysteine rich protein
- Smokers showed higher placental MT and cadmium levels, together with decreased newborn birth weights, as compared to non-smokers (Ronco, et al., 2006)
Cd and Zinc

- Human placenta perfused with high concentrations of cadmium impaired maternal – fetal zinc transfer (Weir, 1990).
- Zinc in umbilical cord is associated with birth weight.
Qualifying study participants (n = 18) were evaluated for ASD severity using the Childhood Autism Rating Scale (CARS) and quantitatively for arsenic, Hg, cadmium, lead, chromium, cobalt, nickel, aluminum, tin, uranium, and manganese using hair toxic element testing by Doctor's Data (a CLIA-approved laboratory). Increasing hair Hg concentrations significantly correlated with increased ASD severity.

Yorbik et al (2010)

- Chromium, cadmium, and lead levels in urine of children with autism and typically developing controls. Urine levels of Cr, Cd, and Pb were measured in 30 children with autism and compared with 20 healthy controls. This study suggested that autism may be associated with significant decrease in excretion rate of Cd and Pb and a significant increase excretion rate in the levels of Cr in the urine.

A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders.


In this study, the concentration of two toxic heavy metals, lead (Pb) and mercury (Hg), were measured in red blood cells, along with detoxifying enzymes (GST), and vitamin E, in the plasma of subgroups of autistic patients with different Social Responsiveness Scale (SRS) and Childhood Autism Rating Scale (CARS) scores. The results were compared to age- and gender-matched healthy controls. RESULTS: The obtained data showed that the patients with autism spectrum disorder had significantly higher Pb and Hg levels and lower GST activity and vitamin E concentrations compared with the controls. The levels of heavy metals (Hg and Pb), GST and vitamin E were correlated with the severity of the social and cognitive impairment measures (SRS and CARS).
Severity of Autism
Background on Environmental Exposures

- Review of handouts
- Toxicants of concern
- Assessment
Vaccinations

- The IOM also recently conducted a review of the current medical and scientific evidence on vaccines and certain health events that may be observed after vaccination. It released a report in August 2011 on 8 vaccines given to children and adults that found the vaccines to be generally safe and serious adverse events following these vaccinations to be rare.

- “The committee concludes that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism. The committee also concludes that the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only.”

Study from the Netherlands

- deCock et al (2012): Positive associations were found for ASD in relation to exposure to all chemicals investigated, which included hazardous air pollutants, pesticides and bisphenol A (BPA).
- Endocrine disruptors may be found in many everyday products— including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides.
Endocrine disruptors are chemicals that may interfere with the body’s endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife.

Examples: Dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers such as bisphenol A.
Air pollution

- Air pollution contains many toxicants known to affect neurological function and to have effects on the fetus in utero.
- Recent studies have reported associations between perinatal exposure to air pollutants and autism spectrum disorder (ASD) in children.
Harvard School of Public Health, Nurses Study II

U.S. Environmental Protection Agency-modeled levels of hazardous air pollutants at the time and place of birth and ASD in the children of participants in the Nurses’ Health Study II (325 cases, 22,101 controls).

Accounted for possible confounding and ascertainment bias by adjusting for family-level socioeconomic status (maternal grandparents' education) and census tract-level socioeconomic measures (e.g., tract median income and percent college educated), as well as maternal age at birth and year of birth.

Also examined possible differences in the relationship between ASD and pollutant exposures by child's sex.

RESULTS:

Perinatal exposures to the highest versus lowest levels of diesel, lead, manganese, mercury, methylene chloride, and an overall measure of metals were significantly associated with ASD, with odds ratios ranging from 1.5 (for overall metals measure) to 2.0 (for diesel and mercury).

In addition, linear trends were positive and statistically significant for these exposures ($p < .05$ for each). For most pollutants, associations were stronger for boys (279 cases) than for girls (46 cases) and significantly different according to sex.

CONCLUSIONS:

Perinatal exposure to air pollutants may increase risk for ASD.
Pesticide exposures

- The interaction of agricultural pesticides and marginal iodine nutrition status as a cause of autism spectrum disorders.
Correlation vs. Causation

- \textit{correlation} and \textit{causation} in scientific and health-related studies. An action or occurrence can \textit{cause} another. If one action causes another, then they are most certainly correlated. But just because two things occur together does not mean that one caused the other.

- \url{http://www.stats.org/faq_vs.htm}
The Pyramid of Environmental Factors Associated with Autism

http://readingroom.mindspec.org/?page_id=4463
The Pyramid of Environmental Factors Associated with Autism

- Each environmental factor is assigned a category based on the number of studies, agreement among studies, and the existence of an established animal model of autism.

- Rare and Direct: Factors rarely encountered but directly linked to autism in numerous, peer reviewed publications and in established animal models.

- Moderately Associated: More than 10 repeated, peer-reviewed publications citing a positive association and/or an established animal model of autism.

- Weakly Associated: Fewer than 10 repeated, peer-reviewed publications citing a positive association OR the existence of numerous discordant studies.
RESOURCES

- CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network
  http://www.cdc.gov/ncbddd/autism/addm.html

- Autism Speaks http://www.autismspeaks.org/